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Genetic invalidation of Lp-PLA₂ as a therapeutic target:

large-scale study of five functional Lp-PLA₂ lowering alleles

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ABSTRACT (248 words)

Aims: Darapladib, a potent inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂), has not reduced risk of cardiovascular disease outcomes in recent randomized trials. We aimed to test whether Lp-PLA₂ enzyme activity is causally relevant to coronary heart disease (CHD).

Methods: In 72,657 patients with CHD and 110,218 controls in 23 epidemiological studies, we genotyped five functional variants, four rare loss-of-function mutations (c.109+2T>C[rs142974898], Arg82His[rs144983904], Val279Phe[rs76863441], Gln287Ter[rs140020965]) and one common modest-impact variant (Val379Ala[rs1051931]) in *PLA2G7*, the gene encoding Lp-PLA₂. We supplemented de-novo genotyping with information on a further 45,823 CHD patients and 88,680 controls in publicly available databases and other previous studies. We conducted a systematic review of randomized trials to compare effects of darapladib treatment on soluble Lp-PLA₂ activity, conventional cardiovascular risk factors, and CHD risk with corresponding effects of Lp-PLA₂-lowering alleles.

Results: Lp-PLA₂ activity was decreased by 64% ($p=2.4\times10^{-25}$) with carriage of any of the four loss-of-function variants, by 45% ($p<10^{-300}$) for every allele inherited at Val279Phe, and by 2.7% ($p=1.9\times10^{-12}$) for every allele inherited at Val379Ala. Darapladib 160mg once-daily reduced Lp-PLA₂ activity by 65% ($p<10^{-300}$). Causal risk ratios for CHD per 65% lower Lp-PLA₂ activity were: 0.95 (0.88-1.03) with Val279Phe; 0.92 (0.74-1.16) with carriage of any loss-of-function variant; 1.01 (0.68-1.51) with Val379Ala; and 0.95 (0.89-1.02) with darapladib treatment.

Conclusions: None of a series of Lp-PLA₂-lowering alleles was related to CHD risk, suggesting that Lp-PLA₂ is not a valid therapeutic target.

KEY WORDS: Human genetics, target validation, coronary heart disease, Lipoprotein-associated phospholipase A₂, darapladib

59 **ABBREVIATIONS**

60 CHD = Coronary Heart Disease

61 CI = Confidence Interval

62 HDL = High-density lipoprotein

63 LDL = Low-density lipoprotein

64 Lp-PLA₂ = Lipoprotein-associated phospholipase A₂

65 MI = Myocardial infarction

66 SD = Standard deviation

67

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69 3 main figures, 2 tables, 1 Appendix

70 Supplement (comprising a supplementary note and 6 tables, 4 figures)

INTRODUCTION

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂), an enzyme expressed by inflammatory cells in atherosclerotic plaques, is carried in the circulation bound predominantly to low-density-lipoprotein (LDL)¹. Lp-PLA₂ (also called platelet-activating factor acetyl hydrolase) hydrolyzes oxidized phospholipids to yield pro-inflammatory products implicated in endothelial dysfunction, plaque inflammation, and formation of necrotic core in plaque¹. Observational² and experimental studies in humans and animals have suggested that Lp-PLA₂ could be a valid therapeutic target, postulating this enzyme to link oxidative modification of LDL and development of inflammatory responses to arterial intima¹. Previous studies have investigated genetic variants altering Lp-PLA₂ function in relation to coronary heart disease (CHD) risk^{3, 4}. However, these studies have generally yielded inconclusive, or conflicting results^{3, 4}, perhaps due to limited statistical power and to limited knowledge about variants altering Lp-PLA₂ function (i.e., previous studies have been able to consider only one loss-of-function variant in *PLA2G7*, the gene encoding Lp-PLA₂).

However, two phase 3 randomized trials of darapladib, a potent inhibitor of Lp-PLA₂ activity, have not shown reductions in cardiovascular risk^{5, 6}. These results could, at least in part, have been due to features of the trials. One of the phase 3 trials was restricted to patients recently hospitalized with acute coronary syndromes⁵, yet many cardiovascular events occurring early after acute coronary syndromes may relate to thrombotic mechanisms and not be modifiable through Lp-PLA₂ inhibition. Trials used statins as background therapy, so any Lp-PLA₂ inhibition achieved with statins could have reduced any incremental benefits of darapladib. Trials could not assess the effects of prolonged Lp-PLA₂ inhibition because they recorded only about 3-4 years of median follow-up^{5, 6}.

An alternative explanation is that darapladib did not reduce cardiovascular risk because Lp-PLA₂ is not a causal risk factor in cardiovascular disease. We tested this possibility by investigating natural loss of Lp-PLA₂ activity. Studies of Lp-PLA₂-lowering alleles should complement randomized trials of darapladib because genotypes are fixed at conception, avoiding potential distorting effects of pre-existing disease and medication usage. Furthermore, Lp-PLA₂-lowering alleles should produce lifelong, rather than shorter-term, Lp-PLA₂ inhibition.

In over 260,000 participants of European, South Asian, or East Asian ancestries, we studied five functional variants in *PLA2G7*. We compared effects of Lp-PLA₂-lowering alleles on soluble Lp-PLA₂ activity, conventional cardiovascular risk factors, and CHD risk with corresponding effects of darapladib, using results from randomized trials.

METHODS

Study design

Figure 1 summarises the study approach. **Table 1** provides definitions and sources of data used. First, we identified four loss-of-function mutations and one missense variant in *PLA2G7* suggested by previous experimental and bioinformatics studies, thereby developing an allelic series for Lp-PLA₂ activity. Second, we assessed associations of these variants — both singly and in combination — with soluble Lp-PLA₂ activity, conventional cardiovascular risk factors, and CHD risk in people of European, South Asian, or East Asian continental ancestries. Third, we compared associations of Lp-PLA₂-lowering alleles with the aforementioned traits and CHD risk with the effects of darapladib treatment through a systematic review of randomized trials.

Genetic variants

We defined loss-of-function variants as non-synonymous variants with *in vitro* or *in vivo* evidence demonstrating complete lack of Lp-PLA₂ activity or sequence changes expected to abolish Lp-PLA₂ function (e.g., nonsense variants or mutations in essential splice sites). We selected variants through a systematic search for loss-of-function variants using the UniProt database⁷, the Exome Aggregation Consortium database (Cambridge, MA, USA; URL: <http://exac.broadinstitute.org>; [accessed November 2014])⁸, studies of site-directed mutagenesis⁹⁻¹¹ and results from targeted gene sequencing¹². Among the full set of variants identified (**eTable1**), we selected the following variants that could be detected in the 1000 Genomes¹³ or the Exome sequencing¹⁴ projects (and, hence, potentially studied at the population level): the splice site mutation 109+2T>C (rs142974898); two non-synonymous variants — Arg82His (rs144983904) and Val279Phe (rs76863441); and the nonsense variant Gln287Ter (rs140020965). These loss-of-function variants are rare in European and South Asian ancestry populations, whereas carriage of 279Phe is common in East Asian ancestry populations and abolition of Lp-PLA₂ activity is well documented¹⁵. Additionally, we studied Val379Ala (rs1051931), a functional variant common in European ancestry populations, which lowers Lp-PLA₂ activity only modestly^{9, 16}, in contrast with the substantial Lp-PLA₂-lowering achieved by the loss-of-function variants described above.

Samples and data for genetic studies

We aimed to maximise study power and comprehensiveness by using the following complementary approaches to generate new data on, as well as to collate systematically existing relevant information about, the *PLA2G7*

variants mentioned above: (1) we conducted de-novo genotyping for 72,657 CHD patients and 110,218 controls (the majority of whom also had information available on some cardiovascular risk factors); (2) we accessed non-overlapping summary-level data from the only known global genetics consortium of CHD¹⁷, yielding information on a further 35,735 CHD patients and 73,481 controls; (3) we conducted a systematic review (supplemented by provision of tabular data from each study investigator) of published East Asian CHD studies of Val279Phe because these studies were not represented in the global CHD consortium, yielding information on a further 10,088 CHD cases and 15,199 controls; (4) we accessed summary-level data from the largest available global genetics consortium on each of several relevant cardiovascular risk factors (eg, Lp-PLA₂ activity, conventional lipids, blood pressure), yielding information on 489,045 participants. Each of these sources of information is summarised below and in **Table 1**.

Coronary heart disease outcomes For CHD outcomes, we had access to data for a total of 92,995 patients and 162,228 controls. For 182,875 of these participants (72,657 CHD patients, 110,218 controls), we did de-novo genotyping of the four loss-of-function variants (c.109+2T>C, Arg82His, Val279Phe, Gln287Ter) and Val379Ala using customized Exome arrays (Illumina, California, USA) by technicians masked to the phenotypic status of the participants' samples. For 35,829 CHD cases, 44,948 controls in eight studies, we had access to individual-participant data. The eight studies were: the Bangladesh Risk of Acute Vascular Events Study (BRAVE)¹⁸, Copenhagen City Heart Study (CCHS)¹⁹, Copenhagen Ischemic Heart Disease/Copenhagen General Population Study (CIHDS/CGPS)¹⁹, European Prospective Investigation into Cancer and Nutrition-Cardiovascular Disease Study (EPIC-CVD)²⁰, MONICA Risk, Genetics, Archiving, and Monograph (MORGAM) study^{21, 22}, Pakistan Risk of Myocardial Infarction Study (PROMIS)²³, Pravastatin in elderly individuals at risk of vascular disease (PROSPER) trial²⁴ and the West of Scotland Coronary Prevention Study (WOSCOPS)²⁵ (these eight studies are collectively called the "CHD Exome+ consortium"). For 15 additional studies (collectively called the "MICAD consortium"), we used similar genotyping methods to those described above but did not genotype c.109+2T>C and had access only to study-level data. We supplemented de-novo data on Val379Ala with non-overlapping consortium-level results from a further 35,735 CHD patients and 73,481 controls in the transatlantic Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAM)²⁶ and Coronary Artery Disease Genetics (C4D)²⁷ consortia (**Table 1**). We obtained tabular data on Val279Phe from seven East Asian studies involving a total of 10,088 CHD cases and 15,199 controls, identified through systematic review (**eTable 5** and **Supplement**). About 90% of CHD patients in our genetic

analysis had myocardial infarction or other major acute coronary events; the remainder had angiographic evidence alone (eg, >50% coronary stenosis; **eTables 2 & 5**).

Lp-PLA₂ activity For 13,835 participants, we had information on functional variants in *PLA2G7* and Lp-PLA₂ activity, using data from de-novo genotyping in MORGAM^{21, 22} and PROSPER²⁴, supplemented by published data from the CHARGE Consortium (ie, from the Atherosclerosis Risk in Communities [ARIC] Study²⁸, Cardiovascular Health Study¹⁶, Framingham Heart Study¹⁶, and Rotterdam study¹⁶), and from 12 East Asian studies identified through the systematic review described above (**Table 1, Supplement & eFigure1, eTables 2-3**).

Conventional cardiovascular risk factors For 177,343 participants, we had information on functional variants in *PLA2G7* and conventional cardiovascular risk factors and several other traits, including circulating concentrations of LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, insulin, and C-reactive protein, and values of systolic and diastolic blood pressure, body-mass index, and estimated glomerular filtration rate. Again, we supplemented data from our de-novo genotyping, with information from existing global genetics consortia (**Table 1, eTables 2-4**).

Randomized trials of darapladib

To compare genetic associations with effects of pharmacological Lp-PLA₂ inhibition, we conducted a systematic review to identify randomized placebo-controlled trials of darapladib that had reported on Lp-PLA₂ activity, conventional risk factors, and/or CHD events (**Supplement**). CHD events in the trials were defined as fatal CHD, MI or urgent revascularisation, as recorded in STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) and in SOLID-TIMI 52 (Stabilization of Plaque Using Darapladib-Thrombolysis in Myocardial Infarction 52)^{5, 6}. We pooled results across trials by fixed-effect inverse-variance weighted meta-analysis (**eFigures 2&3**; see Supplement for details of the methods used).

Statistical methods

We defined effect alleles as those associated with lower Lp-PLA₂ activity and assumed an additive model. For participant-level data, we assessed associations of Lp-PLA₂-lowering alleles with CHD using the genome-wide efficient mixed model analysis, an approach that models each genetic variant as a fixed-effect, but includes both fixed-effect and random-effects of genetic inheritance²⁹ to account for population stratification and relatedness among participants (**Supplement**). The four rare loss-of-function variants were tested jointly within each study

by counting the number of loss-of-function alleles carried by each participant. Log odds ratios and standard errors were meta-analysed across studies using fixed-effect meta-analysis. For studies contributing only study-level data, we performed a similar test by conducting a combined burden test across studies using the R package seqMeta v1.2 (<http://cran.r-project.org/web/packages/seqMeta/>).

We calculated associations of Lp-PLA₂-lowering alleles with soluble Lp-PLA₂ activity and conventional risk factors using linear regression within each study, and then combined the regression coefficients using fixed-effect meta-analysis. When data were missing, we used information on rs1805018 as a proxy for Val279Phe and information on rs7756935 or rs3799277 as proxies for Val379Ala (**Supplement**). To account for population stratification, we adjusted for the first principal component of ancestry (**Supplement**). We calculated risk ratios for CHD with decrements in Lp-PLA₂ activity, dividing the log transformed risk ratio and confidence interval (CI) by the effect on Lp-PLA₂ activity of the instrument (ie, the genetic variant)³⁰. We investigated heterogeneity using the I² statistic. We used Stata 13.1.

RESULTS

Of the 261,950 total participants in this analysis, we studied 195,715 individuals of European ancestry, 34,221 individuals of South Asian ancestry, and 32,014 individuals of East Asian ancestry. In people of European or South Asian ancestry without CHD, the frequency of alleles in *PLA2G7* that lower Lp-PLA₂ activity was 0.005% at c.109+2T>C, 0.04% at Arg82His, 0.04% at Val279Phe, and 0.025% at Gln287Ter (i.e., in aggregate, 0.2% of the European or South Asian participants in the current study carried one of these loss-of-function alleles, although no one carried more than one of these variants), and about 80% at Val379Ala. In people of East Asian ancestry without CHD, the frequency of Val279Phe was about 15% and about 2% of the individuals were homozygous carriers of the 279Phe allele.

Soluble Lp-PLA₂ activity

Compared with non-carriers, homozygote carriers of the 279Phe allele had 94% lower Lp-PLA₂ activity ($p < 10^{-300}$). For each 279Phe allele inherited, Lp-PLA₂ activity decreased by 45% (1.59 SD, 95% CI: 1.61-1.57; $p < 10^{-300}$). In Europeans who inherited any one of the four rare Lp-PLA₂ loss-of-function alleles, Lp-PLA₂ activity decreased by 64% (2.25 SD, 2.68-1.83; $p = 1.6 \times 10^{-25}$). For each 379Ala allele inherited, Lp-PLA₂ activity decreased by 2.7% (0.096 SD, 0.122-0.069; $p = 1.9 \times 10^{-12}$). By comparison, 160mg once-daily darapladib reduced Lp-PLA₂ activity by 65% (2.26 SD, 2.31-2.21; $p < 10^{-300}$). Study-level estimates are provided in **eFigure 2**.

Cardiovascular risk factors

None of the Lp-PLA₂-related variants we studied was significantly associated with values of LDL-cholesterol, HDL-cholesterol, triglycerides, systolic or diastolic blood pressure, body-mass index, estimated glomerular filtration rate, glucose, insulin, and C-reactive protein (**Figure 2**). By comparison, in previous randomized placebo-controlled trials, darapladib did not significantly affect concentrations of LDL-cholesterol or log triglycerides, but could have slightly increased systolic blood pressure and HDL-cholesterol values and slightly decreased C-reactive protein concentration (**Figure 2**).

Clinical CHD outcomes

Compared to non-carriers, the odds ratio for CHD was 0.99 (0.95-1.03) in 279Phe heterozygotes, and 0.93 (0.82–1.05) in 279Phe homozygotes (i.e. nearly complete loss of Lp-PLA₂ function: **Figure 3**). For each loss-of-function (279Phe) allele inherited, the odds ratio for CHD was 0.97 (0.91-1.02; $I^2=30\%$; $P_{\text{Heterogeneity}}=0.2$). In Europeans and South Asians who inherited one of the four rare Lp-PLA₂-loss-of-function alleles, the odds ratio for CHD was 0.92 (0.74-1.16; $I^2=0\%$; $P_{\text{Heterogeneity}}=0.8$; **Figure 3**). For each 379Ala allele inherited, the odds ratio for CHD was 1.00 (0.98-1.02; $I^2=0.0\%$; $P_{\text{Heterogeneity}}=0.5$; **Figure 3**). Study-level results are provided in **eFigure 3**. In sensitivity analyses, odds ratios with each loss-of-function variant were similar to the odds ratio that combined information across the four loss-of-function variants we studied. There was no evidence of heterogeneity in odds ratios between European and South Asian ancestry populations (**eFigure 4**).

Genetic risk ratios for CHD per 65% lower Lp-PLA₂ activity (i.e. the reduction achievable with darapladib treatment) were: 0.95 (0.88-1.03) with Val279Phe in East Asians; and 0.92 (0.74-1.16) with carriage of any one of the four rare variants studied in Europeans and South Asians; and 1.01 (0.68-1.51) with Val379Ala (**Table 2**). By comparison, the risk ratio for CHD with darapladib treatment (i.e. also per 65% lower Lp-PLA₂ activity) was 0.95 (0.89-1.02; **Table 2**).

DISCUSSION

In 2008, GlaxoSmithKline launched a ~\$1 billion program of phase 3 trials of darapladib, a compound which did not reduce cardiovascular event rates in two secondary prevention trials. We tested whether Lp-PLA₂ enzyme activity is causally relevant to CHD by studying five functional alleles that produce widely differing degrees of reduction in Lp-PLA₂ activity. We found that none was related to CHD risk. Hence, our large-scale human genetic data, which are concordant with results from phase 3 trials, suggest that Lp-PLA₂ enzyme activity is not causally relevant to CHD. The implication is that darapladib did not reduce CHD risk in recent trials principally because Lp-PLA₂ is not a valid therapeutic target.

Three features of our study merit comment. First, we studied almost 20 times more CHD patients than the previous largest study of loss-of-function *PLA2G7* alleles, thereby providing the first robust genetic evaluation of effect sizes of Lp-PLA₂ inhibition relevant to phase 3 trials such as relative risk reductions for CHD of 20%. For example, for the Val279Phe variant we had >99% power to detect a 20% risk reduction in CHD for a 65% genetic reduction in Lp-PLA₂ activity (ie, an effect on Lp-PLA₂ activity similar to that achieved by darapladib).

Second, our study has provided the first investigation in CHD of a series of functional alleles that each reduce Lp-PLA₂ function via different molecular mechanisms. Specifically, we studied five different Lp-PLA₂-lowering alleles: three of the alleles were coding variants that produced different amino acid substitutions; two of the alleles produced protein truncations (one due to a nonsense mutation; the other due to a splice-site mutation). Because we observed null and broadly concordant findings for CHD risk across these alleles that each changed the enzyme in a different way, we can more confidently conclude there is no material cause-and-effect relationship. By contrast, when the initial phase 3 trial of darapladib was launched in 2008, only two of the five alleles we studied had yet been identified: data on Val379Ala, a weak effect missense variant, were inconclusive because CHD studies were under-powered³¹; data on Val279Phe, a loss-of-function variant, and CHD risk were sparse and restricted to East Asian populations.

A third feature was our study's analysis of substantial data from three different major ethnic groups: Europeans, South Asians, and East Asians. This ethnic diversity enhanced the generalisability of our results.

Our study had potential limitations. We used the "major coronary events" endpoint from phase 3 darapladib trials for comparison of pharmacological inhibition of Lp-PLA₂ with genetic inhibition, whereas definitions of CHD used in human genetic studies were not strictly uniform (eg, some studies included patients with only

angiographic evidence of CHD). However, about 90% of CHD cases included in our genetic analyses had myocardial infarction or other major acute coronary events.

It could be that cardioprotective benefits of Lp-PLA₂ inhibition were obscured by pleiotropic effects of *PLA2G7* variants; for example, 279Phe is known to produce a misfolded version of Lp-PLA₂ not secreted by cells, prompting suggestions that its carriage could produce “off-target” effects such as increased cell death^{32, 33}. However, because we found null associations between four other functional alleles in *PLA2G7* and CHD, each of which operates via a different molecular mechanism, it argues against this explanation.

Lifelong genetic reductions in Lp-PLA₂ could result in compensatory responses that increase CHD risk. However, this explanation seems unlikely because it would require any such compensation to apply similarly across alleles that produce widely differing degrees of reduction in Lp-PLA₂ activity. Furthermore, any such compensation could not operate through known cardiovascular mechanisms because we observed no associations between Lp-PLA₂-lowering alleles and several established and emerging cardiovascular risk factors.

Soluble enzyme activity could be an imperfect indicator of the relevance of Lp-PLA₂ to atherosclerotic plaques. However, for homozygote carriers of 279Phe, Lp-PLA₂ activity should be almost abolished across all tissues. Finally, we studied life-long genetic reductions in Lp-PLA₂ activity in relation to first-onset CHD outcomes rather than recurrent CHD, whereas darapladib trials studied recurrent coronary events in patients with stable or acute coronary disease.

Our findings suggest that, in retrospect, the lack of efficacy of darapladib in phase 3 trials could, in principle, have been anticipated. However, it is important to acknowledge that the methods and data used in the current analysis were not available at the time the darapladib program was launched. Nevertheless, the current data underscore the growing importance of human genetic approaches to enhance the efficiency of development of medicines by validating (or invalidating) novel drug targets³⁴⁻³⁷. Our results also illustrate how human genetic evidence can assist interpretation of observational epidemiological data. We found that functional alleles in *PLA2G7* do not alter levels of pro-atherogenic lipids (eg, LDL-C). This result suggests that such pro-atherogenic lipids do not mediate associations between Lp-PLA₂ activity and CHD, supporting the need to adjust epidemiological associations of Lp-PLA₂ activity with CHD risk for pro-atherogenic lipids (an approach which yields results consistent with non-causality)².

294 In summary, none of a series of Lp-PLA₂-lowering alleles was related to CHD risk, suggesting that Lp-PLA₂ is
295 not a valid therapeutic target.

296

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303 **DISCLOSURES**

304 Anders Malarstig and Maria Uria-Nickelsen are full time employees of Pfizer. Since October 2015, Daniel
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308

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657 AUTHOR CONTRIBUTIONS:

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659 **FIGURE LEGENDS**

660 **Figure 1:** Summary of study design

661 **Figure 2** Mean per allele differences in Lp-PLA₂ activity and cardiovascular risk factor levels by Lp-PLA₂
662 lowering alleles or with darapladib 160mg daily

663 **Figure 3:** Association of Lp-PLA₂-lowering alleles with Lp-PLA₂ activity and CHD risk

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747 **Table 1:** Definitions and source of contributing data for the main study outcome

Lp-PLA ₂ assessment tool	Val279Phe, Loss-of-function variant common in East Asians‡	Four loss-of-function variants*, rare in Europeans & South Asians†		Val379Ala, modest impact variant				Darapladib
Data sources	Systematic review: Study-level data from up to 12 East Asian studies	De-novo genotyping and participant-level data: up to 8 European or or South Asian ancestry studies from the CHD Exome+ Consortium ¹⁸⁻²⁵ ; De-novo genotyping and study-level data: up to 15 European ancestry studies from the MICAD Exome consortium ³⁷ and 3 European ancestry studies from the CHARGE Consortium ^{16, 28} ; Plus publicly available consortium data						Systematic review: Study-level data from up to 5 randomized clinical trials ^{5, 6, 38-40} from a systematic review
Endpoint								
Coronary heart disease [^]	7 East Asian studies	8 European or South Asian ancestry studies from the CHD Exome+ Consortium ¹⁸⁻²⁵	15 European ancestry studies from the MICAD Exome consortium ³⁷	8 European or South Asian ancestry studies from the CHD Exome+ Consortium ¹⁸⁻²⁵	8 European ancestry studies from the MICAD Exome consortium ³⁷	14 European ancestry studies from the CARDIoGRAM consortium ²⁶	4 European or South Asian ancestry studies from the C4D consortium ²⁷	2 phase III randomized clinical trials of darapladib ^{5, 6}
	10,088 cases 15,199 controls	35,829 cases 44,948 controls	35,533 cases 64,130 controls	32,196 cases 41,464 controls	14,976 cases 32,084 controls	20,315 cases 58,419 controls	15,420 cases 15,062 controls	3364 cases 25,490 non-cases
Lp-PLA ₂ activity ^{\$}	12 East Asian studies	1 European ancestry study from the CHD Exome+ Consortium ²⁴	1 European ancestry study from the CHARGE Consortium ²⁸	2 European ancestry studies from the CHD Exome+ Consortium ^{21, 22, 24}		3 European ancestry studies from the CHARGE consortium ¹⁶		3 phase II randomized clinical trials ³⁸⁻⁴⁰
	8468	1240	8564	2173		11,662		854
Conventional risk factors ^{\$}	12 East Asian studies	8 European or South Asian ancestry studies from the CHD Exome+ Consortium ¹⁸⁻²⁵		8 European or South Asian ancestry studies from the CHD Exome+ Consortium ¹⁸⁻²⁵		Publicly available consortium data		5 randomized clinical trials ^{5, 6, 38-40}
BMI	17,898	76,584		51,201		126,142 from 46 studies from the GIANT Consortium ⁴¹		NA
Blood pressure	6705	72,450		71,256		69,245 from 29 studies from the ICBP Consortium ⁴²		323
Lipids	17,643	76,826		55,431		94,311 from 46 studies from the GLGC Consortium ⁴³		803
C-reactive protein	2914	40,484		41,442		66,185 from 15 studies from the CHARGE Consortium ⁴⁴		848
Glycaemic traits	2914	9420		9408		46,186 from 21 studies from the MAGIC Consortium ⁴⁵		NA
eGFR	4017	32,929		32,190		74,354 from 26 studies from the CKDGen Consortium ⁴⁶		NA

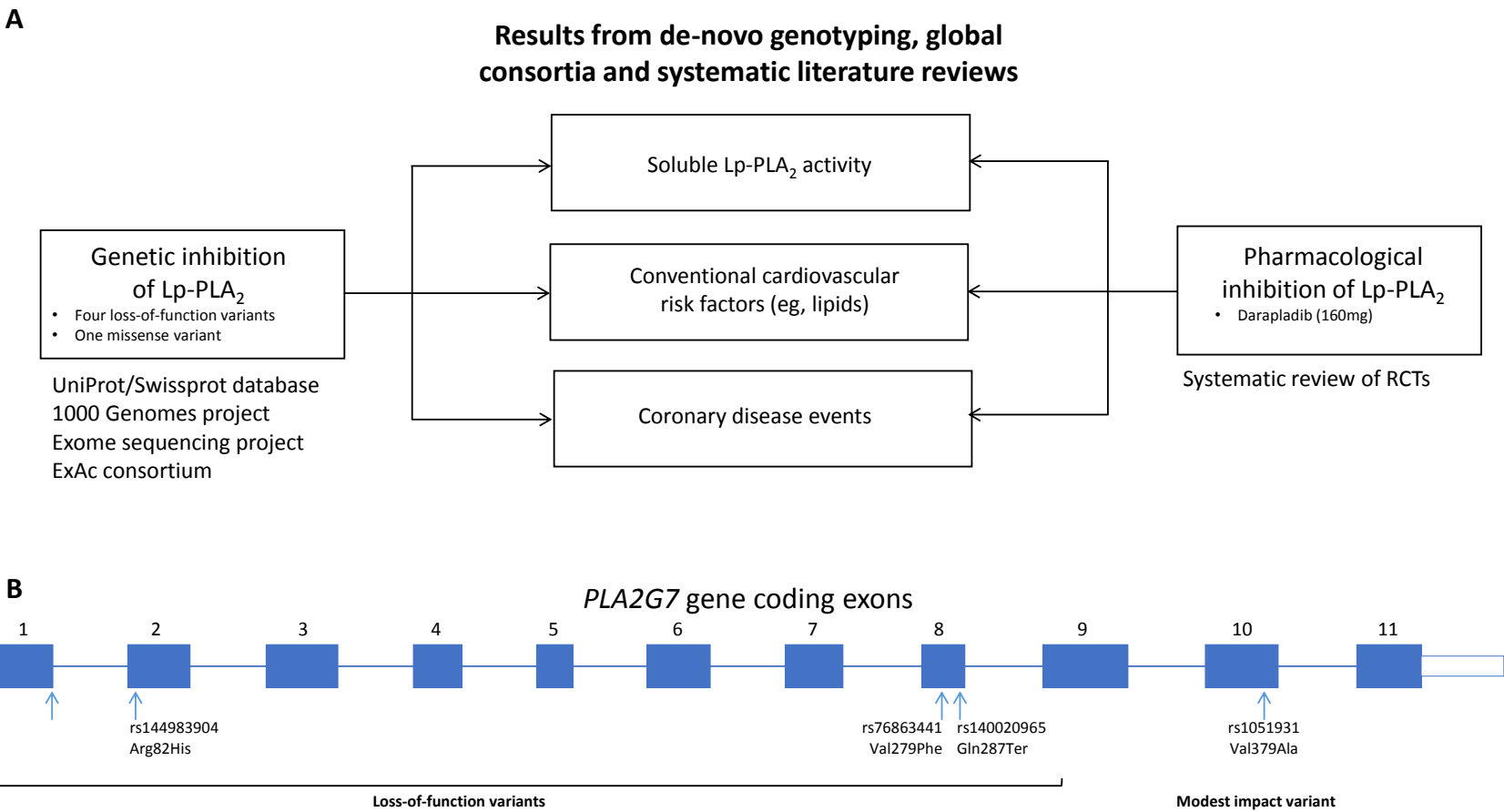
748 ^ In genetic analysis, CHD was defined as myocardial infarction and other major coronary events (~90% of cases) or angiographic stenosis only (~10% of cases) see eTables 2 & 3 for details. In the darapladib analysis CHD was defined as fatal coronary disease, non-fatal MI or urgent
749 revascularization for myocardial ischaemia.
750 \$ See eTables 2 & 3 for details on risk factor measurements
751 rs142974898 (c.109+2T>C), rs144983904 (Arg82His), rs76863441 (Val279Phe), rs140020965 (Gln287Ter); see also **Figure 1B** for further variant details; BMI = Body-mass index, eGFR = estimated glomerular filtration rate, NA= Data not available. Further detail on the individual studies
752 is provided in **eTables 2-3**.
753 CARDIoGRAM=Coronary ARtery DIsease Genome wide Replication and Meta-analysis; CHARGE=Cohorts for Heart and Aging Research in Genomic Epidemiology; CKDGen=Chronic Kidney Disease GENetics consortium; GIANT=Genetic Investigation of ANthropometric Traits
754 Consortium; GLCC=Global Lipids Genetics Consortium; ICBP=International Consortium for Blood Pressure; MAGIC=Meta-Analyses of Glucose and Insulin-related traits Consortium;
755 Consortium;
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	CHD patients	Controls	Risk ratio for CHD per 65% lower Lp-PLA ₂ activity (95% CI)
<i>Genetically lowered Lp-PLA₂</i>			
Val279Phe (East Asian LoF variant)	10,088	15,199	0.95 (0.88 - 1.03)
Four LoF variants*	71,362	109,078	0.92 (0.74 – 1.16)
Val379Ala	82,907	147,029	1.01 (0.68 – 1.51)
<i>Pharmacologically lowered Lp-PLA₂</i>			
Darapladib	3364	25,490	0.95 (0.89 – 1.02)

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* Carriage of any of the four loss-of-function variants c.109+2T>C, Arg82His; Val279Phe; Gln287Ter; LoF = Loss-of-function

761 **Figure 1:** Summary of study design

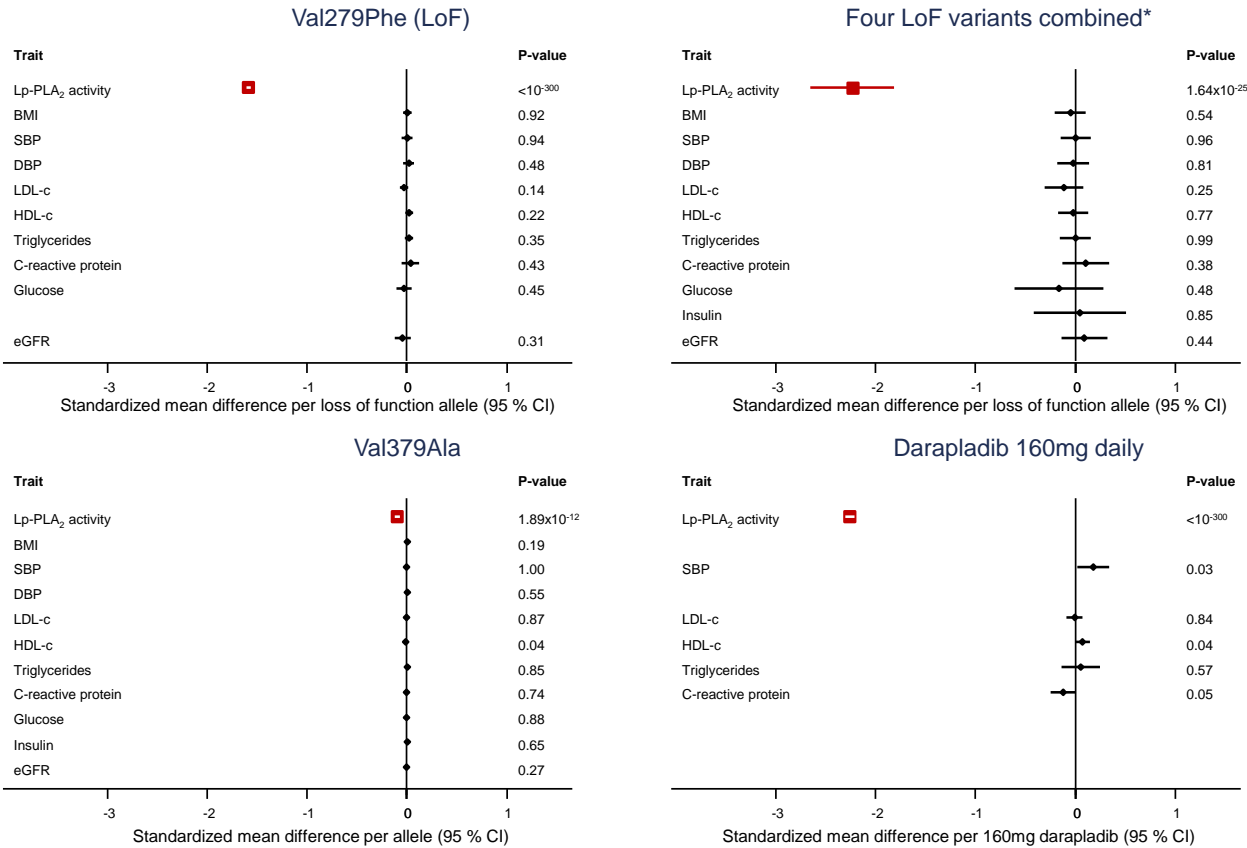


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763 A) Flow chart of study design B) Exonic structure of the *PLA2G7* gene and location of variants used in this study.; ExAc = Exome Aggregation consortium, Lp-PLA₂ = Lipoprotein-associated phospholipase A₂, RCT =

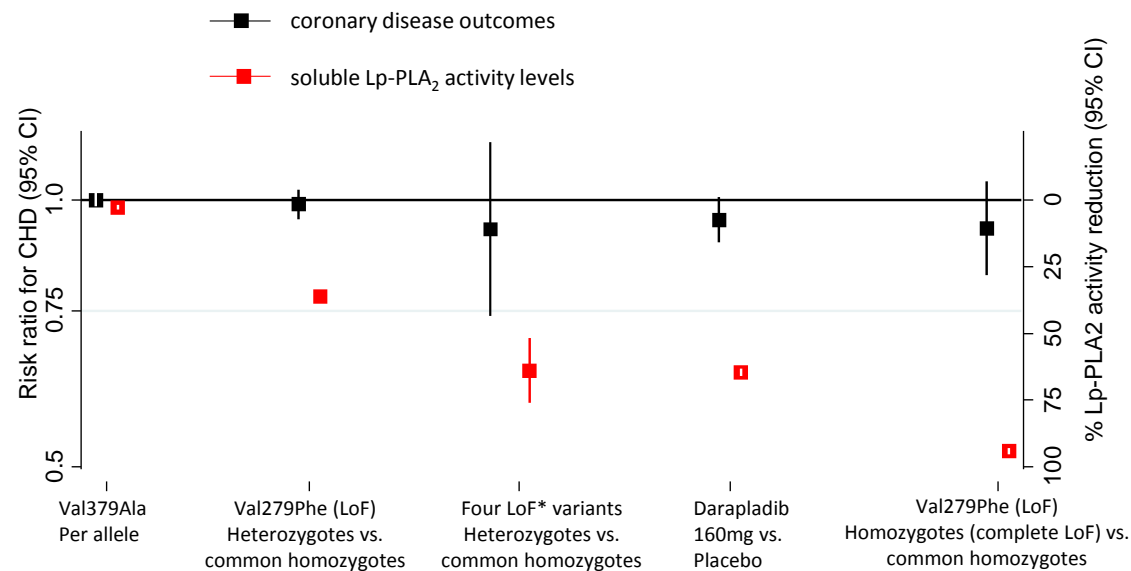
764 Randomized controlled trial, UniProt/Swissprot = Manually annotated and reviewed section of the Universal Protein resource database.

765 **Figure 2**



766 To enable comparison of the magnitude of associations across several different markers, analyses were undertaken with standardized units of measurement for each marker. Associations are presented as per allele
767 change in the biomarker expressed as standard deviations. * Carriage of any of the four loss-of-function variants c.109+2T>C, Arg82His; Val279Phe; Gln287Ter; BMI = Body-mass index, DBP = Diastolic blood
768 pressure, eGFR = estimated glomerular filtration rate, HDL-c = High-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, LoF = Loss-of-function, Lp-PLA₂ = Lipoprotein associated
769 phospholipase A₂, SBP = systolic blood pressure. Numbers of participants are provided in **Table 1**. Details of contributing studies are provided in **eTables 2-3**.
770

771 **Figure 3**



Analysis of coronary heart disease outcomes	Cases	82,907	8789†	71,362	3364	6983†
	Controls	147,029	13,190†	109,078	25,490	10,206†
Analysis of soluble Lp-PLA ₂ activity	Participants	13,835	8264	9804	854	5997

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773 Spectrum of functional alleles in *PLA2G7* and effects on Lp-PLA2 activity (red estimates) and coronary heart disease risk (black estimates); * Carriage of any of the four loss-of-function variants c.109+2T>C,

774 Arg82His; Val279Phe; Gln287Ter; † One study did not provide tabular data to enable calculation of CHD odds ratios in heterozygotes or homozygotes. Hence, numbers are less than those presented for the per allele

775 analysis in **Table 2**; LoF = Loss-of-function

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